Section of Psychiatry.

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Gastro-intestinal Focal Infection in Relation to Oral Sepsis, with special reference to Anaerobes, occurring in Six Cases of Mental Disorder.

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On the subject of focal infection in relation to mental disorders much work has already been done. Cotton, Pickworth [1], Graves [2], McRae and Ford Robertson [3], and others, have contributed largely to our appreciation of its occurrence in certain groups of insanity. I wish here to treat the subject from a somewhat different angle and to include a brief reference to two special groups of bacteria which my father—the late W. Ford Robertson—in his extensive researches, claimed to be of much importance in the causation of mental disease.

Seven years ago, as interim pathologist to the Laboratory of the Scottish Asylums, I had the opportunity of studying Ford Robertson's bacteriological methods. Two years later I became assistant to a consulting pathologist in Lancashire and honorary assistant pathologist and bacteriologist to the Southport Infirmary. There I had the opportunity of carrying out a large number of bacteriological, biochemical and fractional test-meal analyses on non-mental patients, and from this experience I have gained a valuable comparative background of control cases. For the past eighteen months I have put into practice similar lines of investigation on all patients admitted to the New Reception Hospital, Wantage House, St. Andrew's, Northampton. In the time at my disposal it will only be possible to give the main outlines of the results and to indicate conclusions which in some instances are still tentative. The object of this investigation, covering, up to date, 114 cases of mental disorder, was to ascertain the relationship of oral sepsis, in its widest sense, to gastric function, the disorders presented and the state of the intestine, especially the colon, consequent upon these conditions. Anderson [4] in his paper on "Gastric infection secondary to oral sepsis" quotes twenty cases clearly showing the value of test-meal analysis and bacteriological examination of the resting juice.

His group were achylias and four were early cases of mental disorder. He confined his investigation to the question of gastric infection only, but the results help to confirm the fact that not a few suffer from gastric disorders dependent in the first instance on oral sepsis. My own experience amply bears out his conclusions.

It is recognized that gastric efficiency is optimum when sufficient hydrochloric acid and pepsin are secreted to carry out the first stage of digestion, but what is also of importance is that sufficient hydrochloric acid should remain in the stomach after a meal to form a barrier, having a bactericidal action, to organisms swallowed from respiratory or dental infections. A certain proportion of healthy individuals, however, included in the normal standard range, fail to have free hydrochloric acid in the resting juice, and secretion may not begin until three-quarters of an hour afterwards. It will be seen later that the normality of the group is open to question when tested by bacteriological methods.

The technique of the fractional test-meal has been the same for all cases, and the conditions under which the tests have been carried out have been uniform. No

indication of the forthcoming test has been given to the patient, in order to avoid psychic influences which might disturb the gastric mechanism during the last meal (supper) and so possibly affect the state of the resting juice which was to be drawn off twelve hours later. The only diversion in the details of the test proper was the addition of 50 grm. of glucose to the standard salt-free oatmeal gruel, for the purpose of carrying out the glucose-tolerance test simultaneously.

Ryle's tube and a 20-c.c. syringe were sterilized immediately before use. The resting juice was drawn off, every care being taken to secure as much as possible. The sample was then divided, half being placed in a sterile tube for bacteriological examination. After the meal was taken, eight samples of 12 c.c. were drawn off each quarter of an hour and the stomach emptied at two hours and the meal residue measured. The chemical analysis consisted in the estimation of free and combined hydrochloric acid, chlorides, mucus, starch, bile, blood, lactic acid, and pepsin activity of the resting juice and one hour sample.

The bacteriological technique is an elaboration of that carried out by Ford Robertson [5]. For differentiation of streptococci, Warren Crowe's chocolate agar-plates are used and have proved very satisfactory. A large group of streptococci are known as "peroxidase" producers, whose action is to bleach the media surrounding the colony to a yellow or yellow-green colour. They can thus be readily identified. In intestinal culture a work, in which coliform and fæcal types of streptococci usually predominate, the yellow colonies of the respiratory and dental types of streptococci are easily differentiated. The anaerobic technique [6] which I have used now for some years has an essential place in the study of bacteria peculiar to the insane and border-line cases. The details of the methods I have described elsewhere.

A summary of the clinical aspects of the oral condition of the cases under review shows that the existence of tonsillar focal infection is variable. Atrophic and fibrotic inflammatory conditions are by far the most commonly met with. Pus and mucopus in the crypts can usually be found and in many cases Eve's tonsil suction method will extract large cheesy pellets which, on culture, are swarming with bacteria, especially streptococci. Anaerobic culture has yielded diphtheroids in some cases. With regard to the state of the teeth, eleven cases were edentulous and a slightly larger number nearly so. Apical conditions as ascertained by personal radiographic examination are frequently met with. In few cases could the state of the gums be considered perfectly healthy, and cultures taken from pockets around the teeth were almost invariably positive to streptococci and *Micrococcus catarrhalis*.

In all but a few cases the tonsillar or dental resting juice and intestinal cultures have been systematically studied, in an attempt to trace the descent of oral infection from one region of the alimentary canal to another. Out of the 114 cases in which test meals were given ninety-one cultures of the resting juice were made. In about half of these, anaerobic methods were added. In sixty cases where the first culture was positive the resting juice was allowed to stand at room-temperature for twenty-four hours—twice the average fasting period—in order to test its germicidal power. After this period it was then re-cultured, and the growths, if any, compared. Analyses of the results are as follows: Of the forty-seven cases having free hydrochloric acid in the resting juice, 63·8% were sterile on immediate culture, but 91·4%, or an additional 27·6%, were negative when cultured a second time.

The three cases in which the second cultures remained positive had only a trace of free hydrochloric acid in the resting juice. These results show that, provided free hydrochloric acid is present in the resting juice in even moderate degree, bacteria are effectively destroyed. The converse of this is well shown in the forty-four cases without free hydrochloric acid in the resting juice. Only one case produced negative culture, 97·7% being positive. Further, twenty-one out of the forty-four were cultured a second time and all remained highly positive to organisms, demonstrating the

inability of the resting juice to destroy them. In some instances the resting juice flora has proved a more fertile source for varied species of streptococci than the tonsils, especially in edentulous patients or those nearly so. Comparison between the two cultures has shown that the gastric mucous membrane harbours the dental sepsis of years past. Thus, it is possible for some of us to lose our teeth only to maintain the same infection elsewhere. The significance of these findings can be better appreciated when it is realized that the achylic, achlorhydric, and hypochlorhydric groups form 43% of the present cases, and of the latter, 77% have no free hydrochloric acid present in the resting juice, while 32% of the normal group are likewise deficient. In other words, 57% of the cases when judged by the acid tide and peptic activity, can be considered normal, but when viewed in the light of asepsis and sterility, only 50% attain the desired standard.

In considering the significance of the state of the resting juice in relation to bactericidal action, it is realized that gastric function varies from time to time according to the physical and mental state of the individual. Positive variations will be in most instances to his advantage, but loss of secretory function may bring him for days or months into the danger zone of partial anacidity. If this be associated with some toxic condition resulting from oral sepsis, it can be understood how infection of the gastric mucous membrane may come about, and, once established, the tendency will be towards a progressive loss of secretory efficiency, atrophy of the mucous membrane, and the production of achlorhydria.

ANALYSIS OF FRACTIONAL TEST MEAL RESULTS IN 114 CASES OF MENTAL DISORDER.

Average age incidence 41 years.

Group			Percentage
1	Achylia gastrica	5	4·3
2	Achlorhydria	9	7·9
3	Hypochlorhydria	35	30·8
4	Normals	53	46·5
5	Hyperchlorhydria	12	10·5
Special group with no free hydrochloric acid in resting juice, irrespective of group		58	50·8

TABLE SHOWING THE RELATIONSHIP BETWEEN THE GROUPS AND THE ABSENCE OF FREE HYDROCHLORIC ACID IN THE RESTING JUICE.

		Percentage
Hypochlorhydric group	24	77·0
Normal ,,	17	32·0
Hyperchlorhydric ,,	3	25·0

On analysis of the five groups, the results, when compared with the accepted standard of Bennett and Ryle, show one important difference: only 46·5% come within the normal range of acidity, whereas 80% of non-mental individuals come into this range. The onus of this falls on the hypochlorhydrias, which form 30% of the group. The number of achylia gastrica cases is no larger than the accepted incidence in non-mental subjects. The achlorhydric group is also in line with non-mental statistics, but the hyperchlorhydrias are slightly above the normal. Lack of time, unfortunately, prohibits reference and comparisons between the work of others, except the mention of the fact that hypo-acidity has been found by some to be associated with neurasthenia and mental disorders. The main features of each group are as follows:—

(1) *Achylia gastrica* (*five cases*).—Free hydrochloric acid and pepsin were absent throughout. The usual degree of hypermotility was present except in one case. The resting juice was found in small amount and was very mucoid. The meal residue averaged 11 c.c. The quantity of gastric mucus was excessive, averaging 2 + in the eight samples. All the cultures made were highly positive.

(2) *Achlorhydria* (*nine cases*).—Free hydrochloric acid was absent throughout, while peptic activity averaged 1-4 on the one-hour sample but tended to be higher in the resting juice. The amount of resting juice was small and very mucoid, one case

excepted, which had 100 c.c. Excessive salivation accounted for this. The meal residue at two hours was 44 c.c. The quantity of gastric mucus was greater, the average being 3 +, and gastric cells were found in large numbers in the cases examined. Resting-juice cultures were again strongly representative of the mouth flora, and second cultures, where carried out, remained positive.

(3) *Hypochlorhydria (thirty-five cases).*—Free hydrochloric acid was present in small amount and 77% had no free acid in the resting juice. In a fairly large proportion of the cases the lateness of the acid tide is very noticeable. In extreme cases hydrochloric acid failed to appear until the last sample. The average starting point for hydrochloric acid secretion was at one hour. The resting-juice amount was again small, and in many cases mainly mucous. The average meal residue was 47 c.c.

The evidence of gastric catarrh was variable and a few had the normal quantity, the average was just under 2 +, but six cases had as much as 3 + or 4 +. The resting juice cultures again proved positive in the absence of hydrochloric acid.

(4) *Normal group (fifty-three cases).*—32% failed to have free hydrochloric acid in the resting juice, and it was noticeable, as in the last group, that this was usually associated with excessive mucus, which persisted for two or three samples. The appearance of the acid tide coincided with the falling off in the quantity of mucus. The amount of resting juice was slightly higher than in the last group, but the average meal residue was 39 c.c. (rather less). Again, cultures conformed to the presence or absence of the acid barrier action.

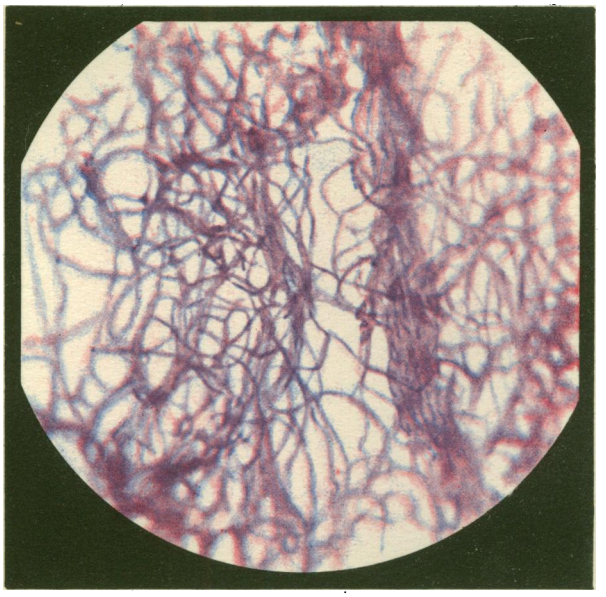
(5) *Hyperchlorhydria (twelve cases).*—In two, the free acid tide rose above 100°, but three had no hydrochloric acid in the resting juice, which was mucoid and small in amount, in spite of every attempt to obtain more. I think in some cases this observation is probably true to fact. They represent the group with the early irritation stage that precedes that of sub-acidity; localized gastritis no doubt would be found in the form of multiple submucous foci, blood or lymphatic borne. The average free acidity at two hours was 85°. The amount of mucus was variable, but smaller than in any of the other groups. Two of the cases show, however, that excessive mucous secretion may occur in hyperchlorhydria and affect the amount of free hydrochloric acid present. Cultures again, were influenced by the presence or absence of free hydrochloric acid.

(6) *The Special Group (fifty-eight cases)* (those having no free hydrochloric acid, irrespective of their group).—These formed 50·8% of the total number. Two points of interest are that 22·8% never secreted free hydrochloric acid, and that in 34% the secretion did not begin until an hour afterwards.

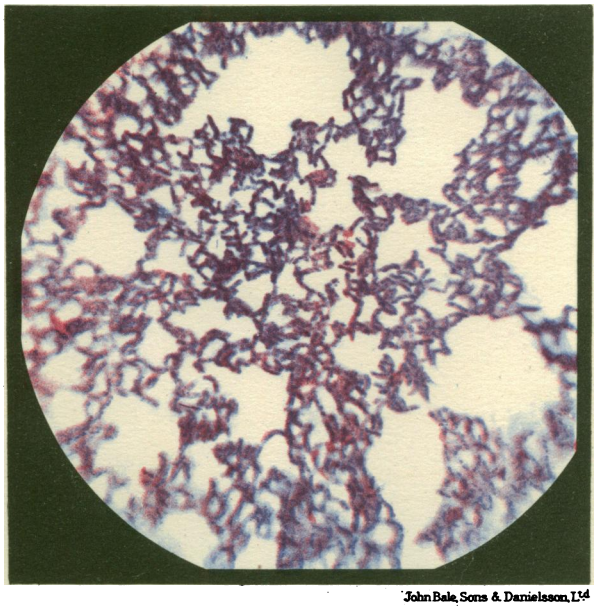
The Intestinal Bacteriological Findings in relation to the Gastric Groups.

Owing to the relative smallness of the anacid and hyperchlorhydric groups, the interpretation of the intestinal cultures in terms of gastric function may not be strictly accurate, but will serve, I think, to indicate the trend of events. From the relationship established between the state of the resting juice, its flora, acidity, and gastric function in general, it would be expected that severe gastric infection would predispose to the descent of catarrhal and dental streptococci into the bowel. Curiously enough, the reverse is the case and is quite contrary to what I myself anticipated. Careful analysis of the intestinal flora by aerobic and anaerobic methods would show, in the present series of cases at least, that the achylic and achlorhydric group have the smallest incidence of peroxidase-producing streptococci—42·9%, and also are found in the least numbers, whereas the hyperchlorhydrics have 66·7% incidence with much greater numbers of colonies.

The explanation of this apparent anomaly is probably as follows: In the anacid group the inherent weakness of the gastric mechanism predisposes to the establishment of chronic and often severe focal infection, to which a general immunity is gained, thus improving the resistance of the lower part of the canal.



No. 53. ×1000. Anaerobic leptothrix isolated from intestine in Case 2. Numerical terms +++



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No. 66. ×1000. Anaerobic metachromatic diphtheroid isolated from tonsils and intestine in Case 1. Numerical terms ++

This is probably compensated for and partially protected by a fully active pancreatic secretory function which by virtue of its trypsin, acts as the second barrier to micro-organisms. In my experience, only one clinical group of non-mental patients fails in this respect, namely, that of severe anæmia and pernicious anæmia. The case for the hyperchlorhydrics is different, without doubt. The full acid tide serves its purpose as a protective barrier, but probably another factor comes into play. Hæmic and lymphatic spread of infection from dental apical conditions, tonsils or glands, must occur more frequently in the members of this group.

The production of gastric and duodenal ulcer is known to start by embolic spread, and my experience of such cases, under parallel methods of investigation, bears out the frequent occurrence of peroxidase streptococci of the *pyogenes* group in the intestine.

It is obvious that the latter type of alimentary infection is more deeply seated, submucous and lymphatic, and therefore more difficult to reach and to treat. My observations on the twelve cases show that they are more chronic in type and tend to be resistive to even specially directed forms of treatment. With regard to fæcal types of streptococci and lactose non-fermenting types of coliforms, the position is not so clear and requires further elucidation.

The Incidence of Anaerobes, especially the Diphtheroid, Lepto-Streptothrix Group.

Tracing the descent of the organisms to the colon in this group is much more difficult, but in some of the cases I have been able to follow them from their origin in either tonsils or teeth to the resting juice, and finally to the intestine, which seems to form an ideal nidus for their growth. The scale of the severity of infection again tends to be definitely upwards as hyperchlorhydric conditions prevail.

This most striking fact emerges: that almost 90% of cases show intestinal infection by one, or a mixture of the three, anaerobic species of bacteria, and 81% give values of 2 + to 4 + in terms of numbers. In other words, the infection in the majority is severe. My experience of some 300 intestinal bacteriological examinations on non-mental patients would show that severe infection by anaerobes of this group is uncommon, but when the neurasthenic or borderland patients (of which I had thirteen) are investigated, they begin to approximate to those now under consideration.

Conclusions based on the 114 Cases under Consideration.

(1) In mental disorders, gastric dysfunction, especially hypochlorhydria, is present to a much greater extent than in normal individuals.

(2) The importance of free hydrochloric acid as a bactericidal barrier has been proved and the relationship between this fact and that of the production of gastritis has been established.

(3) Adequate bacteriological methods show that oral sepsis can be traced throughout the alimentary canal.

(4) The degree of gastric infection does not increase the expectation of invasion of the intestine.

(5) Anaerobic methods are essential if the full significance of the special types of infections present in mental disorders are to be realized.

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The following representative examples of six cases admitted to Wantage House have been chosen. The nature and the course of their infection are illustrated by charts and colour photomicrographs of the micro-organisms isolated:—

Case I (*Severe recurrent confusional*).—C. M. J., female aged 18. Duration of illness, 2½ years. Mental state: Emotional, deluded, and at times hallucinated; recurrent attacks of unconsciousness. Previously to this she became violent and impulsive. Physical: Nutrition poor, general toxæmia, sub-acute tonsillitis, hypochlorhydria, gastritis, Resting juice: No free HCl. Culture positive. Teeth in good condition. Intestinal infection by "peroxidase" streptococci 2 +. Anaerobic culture, diphtheroid and leptothrix bacteria 3 +.

Progress.—Recovery. Able to lead normal family life under guidance. Physical health greatly improved.

Case II (*Melancholia*).—F. G. B., male, aged 54. Duration of illness 14 years. Mental state: Delusions of unworthiness, suicidal tendencies. Physical: Nutrition deficient. Skin sallow, dry; tongue always coated. Edentulous for years. Hyperchlorhydria, gastritis very slight, no free HCl in resting juice. Culture positive. Intestinal flora 3 + "peroxidase" streptococci. Anaerobic culture 4 + diphtheroid and streptothrix. Left hospital after a few weeks.

Case III (*Recurrent confusional*).—T. O. K., male, aged 31. Duration of illness, 11 months. Mental state: At times violent, impulsive, and hallucinated. Physical: Nutrition poor, tongue dirty, breath offensive, constipation severe. Teeth: No apical trouble. Achlorhydria, gastritis severe, resting-juice culture positive. Intestinal cultures, "peroxidase" streptococci, nil. Anaerobic diphtheroids 3 +.

Progress.—Still under treatment; much improved mentally and physically.

Case IV (*Recurrent confusional*).—H., male, aged 29. Duration of illness, 3 years 9 months. Mental state: Periodical attacks of acute confusion, rambling and deluded. Physical: Colour poor. Toxic in appearance and constipated during attacks. Improved in the intervals. Hypochlorhydric, no free HCl in resting juice. Culture positive. Gastritis present. Intestine.—No "peroxidase" streptococci. Anaerobic culture 4 + diphtheroid and leptothrix.

Progress.—Much improved. Attacks ceased, behaviour rational, well physically, very active, still under treatment.

Case V (*Mania*).—V. G., female, aged 47. Duration of illness 2 months. Mental state: Excited, shouting, confused, completely disorientated. Physical: Nutrition poor, very anæmic, under 2,000,000 red blood-cells. Achylia gastrica, resting juice cultures positive. Gastritis present. Teeth: Only lower incisors remain. Intestinal flora, "peroxidase" streptococci 2 +. Anaerobic infection marked.

Progress.—Recovered. Physical condition greatly improved. Red blood-count now 4,700,000.

Case VI (*Systematized delusions*).—O., female, aged 38. Duration of illness three years. Mental state: Refuses food, threatens suicide. Physical: Nutrition very poor, constipation severe. Hyperchlorhydric resting juice. HCl culture negative. Intestinal cultures negative to "peroxidase" streptococci. Anaerobic flora, diphtheroid and leptothrix very profuse.

Progress.—No improvement.

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